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(+)-Camphor Derivative Induced Asymmetric [2 + 2] Photoaddition Reaction

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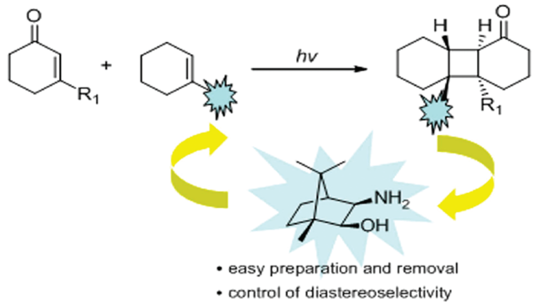
ABSTRACT



An efficient approach to construct an enantiomerically pure cyclobutane skeleton by means of the chiral auxiliary induced [2 + 2] photoaddition reactions has been described. This asymmetric photoreaction exhibited high diastereoselectivity and provided the photoadducts in excellent yields.

Cyclobutanes have been found to be core structural features in a range of naturally occurring and biologically active unnatural products.[1] In addition, the inherent strained cyclobutanes readily undergo transportation to other ring systems by means of certain approaches,[2] which is a particularly efficient strategy for the construction of complex natural product carbon skeletons, such as (+)-elemol,[3] (+)-valeranone,[4] pentalenene,[5] ingenol,[6] ginkgolide B1,[7] and merrilactone A.[8] Therefore, there are myriad methods developed to accomplish the synthesis of these privileged building blocks. Among them, the [2 + 2] photoaddition reaction of olefins has been adopted as the most popular method in this context.[9] In particular,

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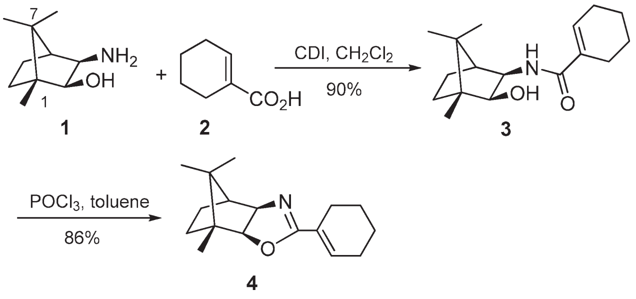
the asymmetric [2 + 2] photocycloaddition reactions, which are known to efficiently prepare the enantiomerically pure cyclobutane scaffold, have attracted considerable research interest from organic chemists.[10,11] For example, several valuable chiral auxiliaries derived from (+)-menthol,[11a,b,d,f,j] tartaric acid,[11i] and naphthalene[11e] have been employed in the asymmetric [2 + 2] photoaddition domain. Despite these advances, the research focused on this issue is still in its early stages and the development of an efficient and practical method is greatly desirable.

With our continuous efforts in the organic photoreactions,[12] we endeavored in exploring an "ideal" chiral auxiliary which features a series of applicability: (i) it can be readily prepared from an available natural source, (ii) easily removed after photoreaction, and (iii) lead to excellent stereoselectivity as well as satisfactory yield. A literature survey showed that a variety of camphor-derived auxiliaries had been widely implemented in the field of asymmetric synthesis in the ground state, such as Diels–Alder reaction,[13] [3 + 2] cycloaddition,[14] aldol addition,[15] Pauson–Khand reaction,[16] Baylis–Hillman reaction,[17] asymmetric cyclopentannelation,[18] etc. We therefore envisioned that natural (+)-camphor derivative **1** might be an optimal candidate to achieve asymmetric induction in organic photochemistry, owing to the steric hindrance originated from the methyl groups on C-1 or/and C-7. To the best of our knowledge, the examples of camphor derivative induced asymmetric photoreactions are still scarce.[11a,h] Herein, we report the asymmetric intermolecular [2 + 2] photoaddition reactions by means of a camphor-derived chiral auxiliary.

Initially, chiral auxiliary **1** was readily prepared in two steps according to the literature procedure starting from natural (+)-camphor,[19] which was then converted to the amide **3** by condensation with carboxylic acid **2** in the presence of carbonyl diimidazole (CDI). Sequential cyclization reaction of **3** with phosphorus oxychloride led to the oxazoline **4**[20] in 86% isolated yield (Scheme 1).

Scheme 1. Synthesis of Compound **4**



With the chiral reactant **4** in hand, the investigation on the photoaddition reaction of **4** with enone **5a**[21] was then carried out using a medium-pressure mercury lamp as a light source through a Pyrex filter ($\lambda > 300$ nm), which was widely used in [2 + 2] photoaddition to minimize the decomposition of adduct products[11] (Scheme 2). To our delight, the reaction occurred smoothly in CH$_2$Cl$_2$ to provide the photoadduct **6a** in 84% isolatd yield after irradiation for 5 h. A mixture of diastereomers of **6a** was observed by NMR analysis, which could not be separated by silica gel column chromatography. The ^{1}H NMR spectra of the diastereomers displayed a similar resonance of the methyne protons at 3.15 ppm (d, J = 11.2 Hz) for H-7 and 2.91 ppm (dd, J = 10.8, 3.6 Hz) for H-8,

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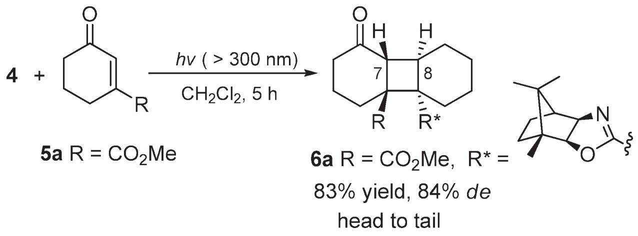
whereas ^{13}C NMR spectra showed two separate resonances of the methyne carbons at 44.9, 44.7 ppm for C-7 and 38.4, 38.3 ppm for C-8. Specifically, the evidence from correlations obtained from an HMQC spectrum allowed signals of C-7 and C-8 to be assigned. In addition, the doublets and coupling constant of 11.2 Hz for H-7 suggested the stereochemistry of adducts **6a** assigned to be *cis-anti-cis* based on the typically *anti* coupling constant.[22]

Scheme 2. Diastereoselective [2 + 2] Photoaddition of **4** with **5a**



On the basis of the above analysis, only the head-to-tail adduct was observed as a single regioisomer in this process. Indeed, the excellent regioselectivity of this reaction was not surprising for us because the similar situation had been well documented in previous work[22] and also could be explained in terms of the transition state analysis on the [2 + 2] photoaddition reaction by Somekawa and coworkers,[23] in which the calculations showed that the transition state energy barriers for the HT adducts were lower than those for the HH adducts, leading to the selectivity preference. However, to our delight, a good diastereoselectivity with an 83% diastereomeric excess (*de*) was achieved by HPLC analysis. In comparison, only a 20% *de* was obtained when the substrate **3** was reacted with **5a** under similar conditions.

Upon initial results, further exploration of reaction conditions was performed for this asymmetric photoreaction procedure. As highlighted in Table 1, the molar ratio of reactants had a significant effect on the reaction results. For example, the poor yields were obtained when the molar ratio of **5a** and **4** was increased from 1:5 to 5:1 even 1:1 (Table 1, entries 2, 3), and the homodimerization product derived from **5a** was observed in this process based upon GC-MS analysis. This might bring about significantly diminished yields during the crossed intermolecular photoaddition of **5a** with **4**. Notably the desired product **6a** formed in this case exhibited an excellent diastereomeric excess (95% *de*) albeit a low yield (7%). Sequential investigations indicated that the reaction occurred smoothly in various solvents without loss of diastereoselectivity coupled with high conversions (Table 1, entries 4, 5).

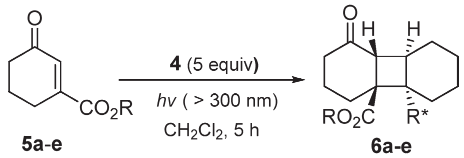
It should be pointed out that a higher diastereoselectivity was obtained as the reaction was conducted at a lower temperature without any decrease in yields (Table 1, entries 6–8). When the reaction was conducted at −20 °C, the best result was achieved in 90% *de* with a 92% isolated yield (Table 1, entry 7). In general, low conversion led to high *de* values in this process (Table 1, entries 8, 9). No significant decrease in *de* value was observed after complete conversion of the substrate **5a** with a prolonged reaction time (Table 1, entry 10).

Table 1. Survey Photoaddition Conditions of **4** with **5a**[a]

entry	molar ratio **5a/4**	solvent[b]	temp	time (h)	yield[c] (%)	*de*[d] (%)
1	1/5	CH_2Cl_2	rt	5	91 (84)	83
2	5/1	CH_2Cl_2	rt	5	7	95
3	1/1	CH_2Cl_2	rt	5	16	94
4	1/5	CH_3CN	rt	5	82	81
5	1/5	C_6H_6	rt	5	89	82
6	1/5	CH_2Cl_2	0 °C	5	90	85
7	**1/5**	**CH_2Cl_2**	**−20 °C**	**5**	**97 (92)**	**90**
8	1/5	CH_2Cl_2	−20 °C	1	45	95
9	1/5	CH_2Cl_2	rt	1	38	87
10	1/5	CH_2Cl_2	rt	10	89	84

[a] Substrate **5a** (0.2 mmol, 0.033 M in solvent). [b] Solvent was purged with N_2 prior to use. [c] Yield determined by GC analysis; isolated yield in parentheses. [d] *De* % analyzed by HPLC on Atlantis dC_{18} column.

Table 2. Survey of Different Carboxylic Ester[a]



entry	R	temp	yield (%)[b]	*de* (%)[c]
1	Me	rt	84, **6a**	83
2	Me	−20 °C	92, **6a**	90
3	Et	rt	83, **6b**	84
4	Et	−20 °C	89, **6b**	93
5	^{i}Pr	rt	76, **6c**	74
6	^{i}Pr	−20 °C	88, **6c**	89
7	Bn	rt	50, **6d**	79
8	Bn	−20 °C	64, **6d**	89
9	(−)-Menthyl	rt	trace, **6e**	–

[a] Substrate **5** (0.2 mmol, 0.033 M in solvent); solvent was purged with N_2 prior to use. [b] Isolated yield. [c] *De* % analyzed by HPLC on Atlantis dC_{18} column.

With the optimized conditions, we investigated the influence of different carboxylic esters **2** on reaction efficiency in this process. As can be seen in Table 2, irradiation of a variety of esters uniformly led to the corresponding products in good yield with 74%−93% *de* values (entries 1−8) except for entry 9 in which only a trace amount of product was obtained due to the steric hindrance.

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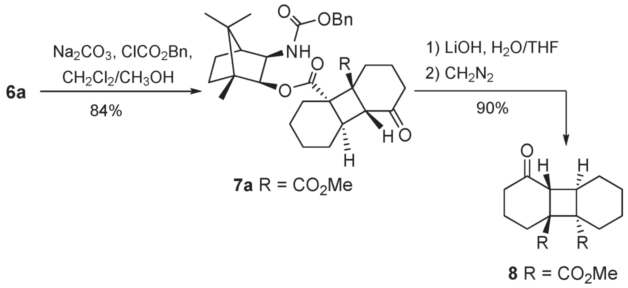
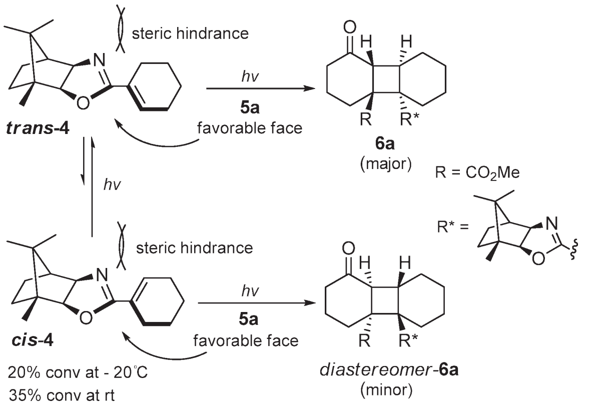
Scheme 3. Removal of the Chiral Auxiliary



To demonstrate the potential applications of this procedure for synthetic transformations, the removal of the chiral auxiliary from a photoproduct was conducted by treatment of photoadduct **6a** with benzyl chloroformate to afford compound **7a** in 84% yield, which was then hydrolyzed with LiOH and esterified with CH_2N_2 to give a carboxylic ester **8** in 90% yield (Scheme 3).

Scheme 4. Proposed Mechanism



Finally, to rationalize the diastereoselectivity observed in the reactions, a plausible mechanism is proposed as depicted in Scheme 4. The excited state **5a** obtained upon UV light irradiation would be preferred to attack from the less sterically congested *endo* face of substrate **4**, which is kinetically controlled to generate **6a** as the major adduct leading to a diastereomeric excess. During the course of photoaddition, the isomerization reaction of *trans*-**4** to *cis*-**4** was observed, in which the photoaddition of **5a** with *trans*-**4** and *cis*-**4** from the *endo* face lead to **6a** and diastereomer-**6a** respectively based upon the diastereoselectivity model (Scheme 4). Obviously, the photoisomerization of **4** could not be excluded from the factors responsible for diminished diastereoselectivity. To add credence to the existence of *cis*-**4** during the reaction, a control experiment was conducted by direct irradiation of *trans*-**4** in the absence of **5a** at room temperature and −20 °C, which led to *cis*-**4** in 35% and 20% conversion respectively (Scheme 4). Such a result is responsible for the fact that lower conversion and temperature led to higher diastereoselectivity. In addition, the computational method was utilized in calculations of the strain energy of the photoproducts **6a**. Based on DFT calculations (B3LYP 6-31 G*), the difference in strain energy between major adduct **6a** and its diastereomer is 2.8 kcal/mol, which means that major adduct **6a** is more thermodynamically stable than its diastereomer and preferred to be formed in the reaction.

In summary, we have developed an efficient approach for asymmetric [2 + 2] photoaddition reactions. This easily enables access to the enantiomerically pure cyclobutanes through the utilization of a chiral auxiliary. Importantly, the natural camphor-derived auxiliary could be introduced and removed through simple synthetic steps. Remarkably, an excellent diastereoselectivity and a synthetically useful isolated yield were afforded in this process. The further application of the chiral auxiliary in other photochemical reactions, as well as in natural product synthesis, is ongoing in our group and will be reported in due course.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.